UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,602	03/30/2005	Kenneth Roux	32376.US	4130

29652 7590 03/21/2008

ENRIQUE G. ESTEVEZ
255 SOUTH ORANGE AVE
SUITE 1401
ORLANDO, FL 32802-3791

EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
03/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,602	ROUX ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,26 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,2 and 4-10* is/are allowed.

6)☒ Claim(s) *3, 11, 26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 March 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-11 and 26-27 are pending.

2. Applicant's election without traverse of Group I in the reply filed on November 19, 2007 is acknowledged.

3. Claims 1-11 and 26-27, drawn to an isolated nucleic acid sequence comprising the nucleotide of SEQ ID NO: 1 or a degenerate variant of SEQ ID NO: 1, expression vector comprising said nucleic acid sequence, culture cell and a method of producing a protein using said nucleotide, are being acted upon in this Office Action.

4. The listing of references in the specification at pages 2-5 is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

5. The disclosure is objected to under 37 CFR 1.821 through 1.825 for failure to supply a sequence identifier to all disclosed sequences. In particular, the primer sequences at page 10, line 6-7, lack a sequence identifier. The particular sequences are not present in the paper copy and computer readable copy of sequence listing. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must provide a *substitute* computer readable form (CFR) copy of the sequence listing, a *substitute* paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same, and where applicable, include no new matter, as required by 37 CFR 1.82(e-f) or 1.825(b) or 1.825(d).

6. The disclosure is objected to because of the following informality: The "SEQ ID NO: 2" in the brief description of drawing for FIGS A1 referring to Ana-o-2 protein is inconsistent with the SEQ ID NO: 2 in the sequence listing. In particular, both SEQ ID NO: 1 and SEQ ID NO: 2 listed in the Sequence Listing are polynucleotide. However, the Brief description of drawing

states: "FIGS. 1 A1 and 1A2, respectively, show the nucleotide sequence encoding for the polypeptide of SEQ ID NO: l, referred to as Ana-o-2, including a stop codon shown underlined and in bold; and the polypeptide of SEQ ID NO:2, which is a tail for the polypeptide of SEQ ID NO: l". The *polypeptide* of SEQ ID NO: **1** at page 6, line 5 and at page 6, line 7 of the specification is inconsistent with the *nucleotide* sequence of SEQ ID NO: **1** in the sequence listing. In the sequence listing, both SEQ ID NO: 1 and 2 are nucleotide sequence. Correction is required.

7. The drawings are objected to because illegible text in Figure 3, and skewed/slated image of FIG. 1A1 is cut off at the sides. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 3, 11, 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated nuclei acid comprising the nucleotide sequence of SEQ ID NO: 1 or a degenerate variant thereof that encodes a cashew polypeptide Ana-o-2 comprising the amino acid sequence of SEQ ID NO: 3, (2) an isolated nucleic acid encoding the amino acid sequence of SEQ ID NO: 3, (3) an isolated nucleic acid encoding a peptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 4-25, (4) an expression vector comprising any of the nucleotide sequence mentioned above, a cultured cell comprising said vector and a method of producing said polypeptide comprising culturing said host cell under conditions permitting expression of said polypeptide, **does not** reasonably provide enablement for (1) any nucleic acid comprising SEQ ID NO: 1 having at least one mutation selected from a deletion, a substitution, and an addition (claims 3 and 27), (2) any degenerate variant thereof that encodes any polypeptide *comprising* at least one amino acid sequence selected from SEQ ID NOS: 4-25(claim 11), (3) any degenerate variant which encodes a polypeptide consisting essentially of an amino acid sequence selected from SEQ ID NOS: 4-25 (claim 26), and (4) any isolated nucleic acid sequence according to SEQ ID NO: 1 or any degenerated variant thereof which encodes any polypeptide consisting essentially of an amino acid sequence selected from SEQ ID NO: 3-25 further comprises one or more deletion, substitution or addition (claim 27). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The claims are drawn to any variant of SEQ ID NO: 1 having one or more deletion, substitution, or addition thereof, any degenerate variant that encodes any polypeptide "comprising" at least one amino acid sequence selected from SEQ ID NO: 4-25 which are fragments of SEQ ID NO: 3, any degenerate variant which encodes any polypeptide consisting

essentially of an amino acid sequence of SEQ ID NO: 4-25, and any nucleic acid encoding any polypeptide consisting of an amino acid sequence selected from SEQ ID NO: 3-25 further comprises any one or more deletion, substitution or addition. The scope of the claims includes numerous structural variants thereof, and the genus is highly variable because a significant number of structural differences between genus members is permitted.

Enablement is not commensurate in scope with how to make and use any variants mentioned above having one or more deletion, substitution, or addition thereof.

There is no definition of "degenerate variant" in the specification as originally filed. The broadest reasonable interpretation of such is that the claims read on all functionally equivalent polynucleotides having any deletion, substitution or addition thereof. The specification discloses only one polynucleotide comprising the nucleotide sequence of SEQ ID NO: 1 encoding cashew nut allergen Ana-o-2 comprising the amino acid sequence of SEQ ID NO: 3. The specification further discloses various linear IgE epitopes from cashew nut allergen Ana-o-2 consisting of the amino acid sequence selected from the SEQ ID NO: 4-25.

However, the instant specification does not teach the structural features, nucleotide sequences, and/or biological functions that are commonly possessed by members of each claimed genus. The specification does not provide any specific guidance as to what changes should be made to SEQ ID NO: 1, the polypeptide of SEQ ID NO: 3-25, and the coding sequences thereof.

There is no guidance as to any functional equivalents, nor derivatives, nor are there any working examples of altered sequences that retain Ana-o-2 function.

It is well known in the prior art that the amino acid sequence of a protein determines the protein's structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence to obtain a desired biological activity requires knowledge and guidance regarding specific amino acid residue(s) in the protein's amino acid sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification) and detailed knowledge of the protein's structure, and the ways in which the protein's structure relates to its function.

Chica et al. (Curr Opin Biotechnol. 2005 Aug;16(4):378-84; PTO 892) teaches that the complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational enzyme modification and design, where rational enzyme modification and design requires in-depth understanding of structure/function relationships.

The positions within a protein's amino acid sequence where modifications can be made with a reasonable expectation of success in obtaining a protein having the same biological activity are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof.

Methods for isolating or generating variants and mutants using random mutagenesis techniques were known in the art. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for altering the protein comprising an amino acid sequence of SEQ ID NO: 3 and its encoding polynucleotide of SEQ ID NO: 1 with an expectation of obtaining a protein derivative and its encoding gene derivative having the same biological activity. At the time of the invention, there was a high level of unpredictability associated with altering a protein sequence with an expectation that the protein will maintain the same desired biological activity. For example, Witkowski et al. (Biochemistry. 1999 Sep 7; 38(36): 11643-50; PTO 892) teaches that only a single amino acid substitution results in conversion of the activity of a protein to a second, distinct activity (see e.g., Table 1, page 11647).

In addition, Stanley et al (Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 892) teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley et al also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. Stanley et al conclude that there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

With respect to degenerate variant which encodes a polypeptide comprising at least one amino acid sequence selected from SEQ ID NO: 4-25, these polypeptides of SEQ ID NO: 4-25 are fragments of SEQ ID NO: 3. The term "comprising" is open-ended. It expands the amino acid sequence of SEQ ID NO: 4-25 to include additional amino acids at either or both ends. There is a lack of guidance as to what amino acids to be added, the coding sequence encoding

such, let alone any nucleic acid further comprises one or more deletion, substitution, or addition thereof.

Given the lack of guidance as to functional variants, the lack of direction or working examples, the breadth of the claims, which encompass innumerable possible nucleic acid sequence encoding proteins, and the amount of experimentation required to determine each possible species individually, it would require undue experimentation to use the invention in a manner commensurate in scope with the claims. Accordingly, enablement is not commensurate in scope with claims that encompass 'degenerate variant' of SEQ ID NO: 1 or SEQ ID NO: 2 or any degenerate variants that encode any polypeptide comprising the amino acid sequence of SEQ ID NO: 3-25 and any degenerate variant comprising any mutation selected from deletion, substitution and/or addition thereof.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

11. Claims 3, 11, 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any nucleic acid comprising SEQ ID NO: 1 having at least one mutation selected from a deletion, a substitution, and an addition (claims 3 and 27), (2) any degenerate variant thereof that encodes any polypeptide *comprising* at least one amino acid sequence selected from SEQ ID NOS: 4-25(claim 11), (3) any degenerate variant which encodes a polypeptide consisting essentially of an amino acid sequence selected from SEQ ID NOS: 4-25 (claim 26), and (4) any isolated nucleic acid sequence according to SEQ ID NO: 1 or any degenerated variant thereof which encodes any

polypeptide consisting essentially of an amino acid sequence selected from SEQ ID NO: 3-25 further comprises one or more deletion, substitution or addition (claim 27).

According to MPEP 2163, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v.Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed.Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116.

The claims are drawn to any isolated nucleic acid sequence comprising the nucleotide sequence of SEQ ID NO: 1 or any variant of thereof having one or more deletion, substitution, or addition thereof. The scope of the claims includes numerous structural variants thereof, and the genus is highly variable because a significant number of structural differences between genus members is permitted.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

The specification discloses only one isolated polynucleotide comprising the nucleotide sequence of SEQ ID NO: 1 which encodes a cashew nut allergen designated as Ana o2 polypeptide comprising the amino acid sequence of SEQ ID NO: 3. The specification discloses IgE epitope from Ana o2 peptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 4-25.

However, the instant specification does not describe and define any structural features, amino acid sequences, nucleotide sequences, and/or biological functions that are commonly possessed by members of each claimed genus. The specification does not provide any specific guidance as to what changes should be made to SEQ ID NO: 1 and SEQ ID NO: 3. There is a lack of specific guidance and disclosure as to which amino acids, the corresponding nucleotides within the full-length sequence of SEQ ID NO: 1 can be substituted, deleted, or added such that the resulting nucleic acid still maintain structure and function as protein encoded by SEQ ID NO:

1. The specification does not describe any biological function for the claimed derivative or fragment of the claimed nucleic acid.

The specification fails to disclose a representative number of species of each claimed genus, which includes many members with widely differing structural, chemical, and biological functions. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In this case, the isolated polynucleotide comprising SEQ ID NO: 1 encoding the amino acid sequence of SEQ ID NO: 3 is insufficient to be representative of the attributes and features common to all the members of the claimed genus of derivatives having any biological activity. Thus, one skilled in the art cannot visualize or recognize the identity of members of each claimed genus.

Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, nucleotide sequence of SEQ ID NO: 1 is insufficient to describe the genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The skilled artisan cannot envision the detailed chemical structure of the encompassed degenerate variants comprising one or more mutation such as deletion, substitution and/or addition, regardless of the complexity or simplicity of the method of isolation. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceuticals Co. LTd., 18 USPq2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's

were found unpatentable due to a lack of written description for the broad class. The specification provided only the bovine sequence.

In this case, the specification provides only one isolated nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1 encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 3, an expression vector comprising the polyncleotide sequence of SEQ ID NO: 1, host cell comprising the vector mentioned above and a method of producing a polypeptide comprising culturing said host cell under conditions permitting expression of a polypeptide encoded by SEQ ID NO: 1.

With respect to degenerate variant which encodes a polypeptide comprising at least one amino acid sequence selected from SEQ ID NO: 4-25, these polypeptides of SEQ ID NO: 4-25 are fragments of SEQ ID NO: 3. The term "comprising" is open-ended. It expands the polypeptide fragment selected from the group consisting of SEQ ID NOS: 4-25 to include additional amino acids at either or both ends. The specification fails to describe what amino acids to be added, much less nucleic acid encoding such polypeptides. Further, the specification does not disclose what modification can be made to any polypeptide of SEQ ID NO: 4-25 such as deletion, substitution and/or addition, the coding sequence thereof and what function the resulting modified peptide has.

Therefore, only an isolated nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1 encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 3, an isolated nucleic acid encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 3, and an isolated nucleic acid encoding a peptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 4-25, an expression vector comprising the polyncleotide sequence of SEQ ID NO: 1, host cell comprising the vector mentioned above and a method of producing a polypeptide comprising culturing said host cell under conditions permitting expression of a polypeptide encoded by SEQ ID NO: 1, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The specification discloses only one polynucleotide comprising nucleic acid sequence of SEQ ID NO: 1 encoding cashew nut allergen Ana-o-2 of SEQ ID NO: 3, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of nucleic acid to describe the genus. Thus, Applicant was not in possession of the claimed

genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).* Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

13. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

14. Claims 3 and 27 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,362,399 (filed June 30, 1998; PTO 892).

The '399 patent teaches an isolated an isolated nucleic acid sequence such as SEQ ID NO: 13 that has more than one deletions and substitution as claimed in SEQ ID NO: 1 (see reference SEQ ID NO: 13 and alignment below, in particular).

```
Qy          1 CTTTCGTGTTGCTTTTTAATTCTCTTTCATGGTTGCCTAGCTT---CTCGCCAGGAATGG 57
              |||||  |||| ||| |   ||  ||  |     | ||| | ||||    |   |    ||     |
Db         16 CTTTCCCTTTGTTTTCTGCTTTTCAGTGGCTGCTGCTTCGCTTTCAGTTTCAGAGAGCAG 75

Qy         58 CAACAACAAGATGAGTGCCAAATCGATAGGCTGGATGCCCTTGAACCGGATAACCGAGTT 117
                | ||| ||| | |||||||| ||| |   | ||  |||||||  |||| ||||||||  |
Db         76 CCACAGCAAAACGAGTGCCAGATCCAACGCCTCAATGCCCTAAAACCGGATAACCGTATA 135

Qy        118 GAGTATGAAGCCGGTACGGTGGAAGCCTGGGATCCTAACCATGAGCAATTCCGATGCGCT 177
              ||||  ||||  ||    | ||   | ||| | |||||| |  ||| |||||  || ||
Db        136 GAGTCAGAAGGTGGCTTCATTGAGACATGGAACCCTAACAACAAGCCATTCCAGTGTGCC 195
```

```
Qy       178 GGTGTTGCCTTGGTTAGGCATACCATCCAACCTAATGGCCTCTCTTGCCTCAATATTCT 237
Db       196 GGTGTTGCCCTCTCTCGCTGCACCCTCAACCGCAACGCCCTTCGCAGACCTTCCTACACC 255

Qy       238 AATGCTCCTCAACTTATTTACGTTGTCCAGGGTGAGGGTATGACAGGAATATCATATCCA 297
Db       256 AACGCTCCCCAGGAGATCTACATCCAACAAGGTAGTGGTATTTTTGGCATGATATTCCCG 315

Qy       298 GGATGCCCAGAAACTTACCAAGCGCCCCAACAGGGACGACAACAGGGACAGAGTGGTAGG 357
Db       316 GGTTGTCCTAGCACATTTGAAGAGCCTCA---------ACAAAAAGGACAAAGCAGCAGG 366

Qy       358 TTCCAGGGACCGGCATCAAAAGATTCGACGCTTCCGTCGAGGCGATATCATCGCAATCCCC 417
Db       367 CCCCAAGACCGTCACCAGAAGATCTATCACTTCAGAGAGGGTGATTTGATTGCAGTGCCA 426

Qy       418 GCCGGAGTAGCACACTGGTGCTACAACGAGGGCAATTCCCCGGTCGTCACTGTTACTCTT 477
Db       427 ACCGGTTTTGCATACTGGATGTACAACAATGAAGACACTCCTGTTGTTGCCGTTTCTCTT 486

Qy       478 CTAGACGTCTCAAACAGTCAAAATCAGCTTGATAGGACCCCACGAAAATTCCATCTGGCT 537
Db       487 ATTGACACCAACAGCTTCCAGAACCAGCTCGACCAGATGCCTAGGAGATTCTATCTTGCT 546

Qy       538 GGTAACCCAAAAGATGTGTTCCAGCAG---------------------------------- 564
Db       547 GGGAACCAAGAGCAAGAGTTTCTACAGTATCAGCCACAGAAGCAGCAAGGAGGTACTCAA 606

Qy       565 ------------------CAGCAACAACACCAATCTCGCGGGCGTAACCTTTTTCTGGC 606
Db       607 AGCCAGAAAGGAAAGCGTCAGCAAGAAGAAGAAAACGAAGGAGGCAGCATATTGAGTGGC 666

Qy       607 TTCGATACAGAGTTATTGGCTGAGGCTTTCCAAGTGGACGAACGTCTCATAAAGCAGCTC 666
Db       667 TTCGCCCCGGAATTCTTGGAACATGCGTTCGTCGTGGACAGGCAGATAGTGAGAAAGCTA 726

Qy       667 AAAAGCGAGGACAACAGGGGTGGCATTG------TTAAGGTGAAGGATGACGAACTTCGG 720
Db       727 CAAGGTGAGAACGAAGAGGAAGAGAAGGGTGCCATTGTGACAGTGAAAGGAGGTCTCAGC 786

Qy       721 GTGATCCGCCCATCAAGGAGTCAGAGCGAGCGTGGAAGTGAGAGTGAAGAGGAAAG---- 776
Db       787 GTGATAAGCCCACCCACGGAAGAGCAGCAACAAAGACCCGGAAGAAGGAGAAGCCAGAT 846

Qy       777 -----TGAGGATGAAAAACGCCGATGGGGACAGCGTGACAATGGGATTGAAGAGACCATT 831
Db       847 TGTGACGAGAAAGACAAACATTGCCAAAGCCAAAGCAGAAATGGCATTGACGAGACCATT 906

Qy       832 TGCACTATGAGACTCAAAGAGAATATCAATGATCCTGCTCGCGCTGACATTTACACCCCA 891
Db       907 TGCACAATGAGACTTCGCCACAACATTGGCCAGACTTCATCACCTGACATCTTCAACCCT 966

Qy       892 GAAGTCGGTCGTCTTACCACACTCAACAGCCTCAACCTCCCAATCCTCAAATGGCTTCAA 951
Db       967 CAAGCTGGTAGCATCACAACCGCTACCAGCCTCGACTTCCCAGCCCTCTCGTGGCTCAAA 1026

Qy       952 CTCAGTGTTGAAAAGGGTGTGCTATACAAAAATGCTCTAGTGCTGCCACACTGGAACCTC 1011
Db      1027 CTCAGTGCCCAGTTTGGATCACTCCGCAAGAATGCTATGTTCGTGCCACACTACAACCTG 1086

Qy      1012 AACTCGCACAGCATAATATACGGGTGCAAGGGTAAAGGCCAGGTTCAAGTAGTAGACAAC 1071
Db      1087 AACGCAAACAGCATAATATACGCATTGAATGGACGGGCATTGGTACAAGTGGTGAATTGC 1146

Qy      1072 TTCGGCAACAGAGTGTTCGACGGCGAAGTCCGCGAGGGACAGATGTTTGGTGGTGCCACAA 1131
Db      1147 AATGGTGAGAGAGTGTTTGATGGAGAGCTGCAAGAGGGACAGGTGTTAATTGTGCCACAA 1206
```

```
Qy      1132 AACTTTGCAGTAGTGAAACGTGCAAGAGAGGAAAGATTCGAATGGATTTCTTTCAAGACC 1191
             ||||||||| || | |  | |  ||  |  || |  ||||| |   |||| |||||||||
Db      1207 AACTTTGCGGTGGCTGCAAGATCACAGAGCGACAACTTCGAGTATGTTTCATTCAAGACC 1266

Qy      1192 AATGATCGGGCCATGACGAGTCCTCTCGCTGGACGCACCTCGGTGCTTGGTGGCATGCCA 1251
             ||||||  |  ||  ||   |    || || ||    | |||  || |    |   ||||
Db      1267 AATGATAGACCCTCGATCGGCAACCTTGCAGGTGCAAACTCATTGTTGAACGCATTGCCG 1326

Qy      1252 GAGGAAGTGTTAGCCAATGCGTTCCAGATCTCAAGAGAAGATGCTAGGAAGATCAAGTTC 1311
             |||||||||  |    |  ||  |  |  ||  |  ||  |  | ||| || ||||| |
Db      1327 GAGGAAGTGATTCAGCAAACTTTTAACCTAAGGAGGCAGCAGGCCAGGCAGGTCAAGAAC 1386

Qy      1312 AACAATC 1318
             ||||| |
Db      1387 AACAACC 1393
```

Thus, the reference teachings anticipate the claimed invention.

15. Claims 1-2, and 4-10 are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
March 14, 2008